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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,341	12/07/2001	Rolando Perex Rodriguez	024518-00003	9449

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 10/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,341	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 34-99 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 34-99 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim 1-33 have been canceled. Claims 34-99 have been added and are under consideration. All species of the Election Requirement of August 2004 are rejoined for examination at this time.

Sections of Title 35, U.S. Code, not found in this action can be found in a previous action.

Claims 34-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) It is unclear if the multiple recitations of "an" RTK receptor or ligand in the claims refers to the same RTK receptor and/or ligand. For purpose of examination, multiple recitations of "an" RTK receptor or ligand will be read as "said" RTK receptor or ligand.

(B) The recitation of "said first agent" and "said second agent" in claim 75 lacks antecedent basis in claim 74.

(C) Claim 70 requires that "said Mab is directed against the EGF receptor and its ligands". It is unclear if a single Mab is meant to satisfy this limitation, or if the claim permits the inclusion of two Mab.

(D) It is unclear how claims 87 and 88 further limit claim 85. Claim 85 recites a vaccine which induces antibodies against an RTK receptor. Claim 87 and claim 88 require conjugates of a RTK ligand, which would induce antibodies against the ligand rather than the receptor.

(E) It is unclear how claims 90-92 further limit claim 89. Claim 89 is depend upon claim 85 which recites a vaccine which induces antibodies against an RTK receptor. Claims 90-92 require a vaccine comprising TGF-alpha, a ligand of a PTK receptor which would be expected to induce antibodies against the ligand rather than the RTK receptor as required by claim 85.

Claims 38, 50, 56, 84, 94, 95 and 97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 38, 50, 56, 97 require antibodies which have the same binding specificities as Ior-R3 and EGF-1. The specification as filed provides support only for the use of IOR-R3 and EGF-1 directly in the claimed compositions, not indirectly for the identification of other antibodies with the same binding specificities.

Claim 84 lacks support in the specification and claims as originally filed for the sequential administration of a vaccine which induces antibodies to a ligand of an PTK receptor and a vaccine which produces antibodies to a second ligand of the PTK receptor.

Claims 94 and 95 lacks specific support in the specification and claims as originally filed for a "container".

Claims 34, 38-40, 50-52, 56-70, 71, 73-83, 85-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods vaccines in which the active principle is EGF or TGF-alpha conjugated to a foreign T-helper cell peptide, for the induction of antibody response against EGF or TNF-alpha, which is a neutralizing antibody response, does not reasonably provide enablement for methods or compositions requiring vaccines comprising as the active agent protein receptors for the induction of antagonistic antibodies to said receptors, or immunotherapy compositions comprising antibodies which competitively inhibit the binding of IOR R3 or EGF-1 to the EGF receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered

in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

(A) As drawn to combinations requiring PTK receptors as the active principle or PTK ligands other than EGF or TGF-alpha.

The instant claims encompass an antibody which binds to a protein tyrosine kinase receptor or an antibody which binds to a ligand of a protein tyrosine kinase receptors in combination with a vaccine in which the active principle is a protein tyrosine kinase receptor. Fong et al (US 2003/0219380) teach that protein tyrosine kinases (PTKs) such as EGFR, APMIS, HER2, PDGF-R and c-met are directly associated with the cell proliferative disorders and the development of cancers and are over-expressed in many tumors and/or persistently activated by autocrine loops. Fong et al teach that PTK over-expression and autocrine loop stimulation account for the most common and severe cancers. Thus, one of skill in the art would reasonable conclude that a vaccine which elicits an antibody which is capable of neutralizing the activity of the tyrosine kinase receptor ligand would be effective at interrupting the autocrine loop on which the cancer cells depend. One of skill in the art would also reasonable conclude that vaccine which elicit antagonistic antibodies that bound to the tyrosine kinase receptors and blocked the endogenous effect of the autocrine/paracrine ligands and did not activate the receptor upon binding would be effective at interrupting the autocrine loop on which the cancer cells which over express said receptors depend. The specification does not teach how to make a vaccine which would elicit an antagonistic antibody against a tyrosine kinase receptor, or a neutralizing antibody against a tyrosine kinase receptor ligand which was not a small peptide. Both the art and the instant specification teach that it is necessary to provide an foreign T-cell helper epitope, usually from an immunogenic bacterial antigen, in order to induce a humoral immune response against a "self" antigen (Grimes et al, US 6,783,761). The prior art also teaches vaccines which elicit antibodies against EGF, wherein EGF is conjugated to a foreign T-cell helper epitope (US 5,894,018). It is noted that EGF is a 53 amino acid peptide. Other tyrosine kinase receptor ligands and the tyrosine kinase receptors themselves are much bigger

than EGF or TGF-alpha, for instance hepatocyte growth factor, or scatter factor, is a 723 amino acid ligand for its receptor c-met which is 1390 amino acids long; PDGF-B, is a 226 amino acid ligand responsible for neoplastic activity at the 1106 amino acid PDGF receptor. One of skill in the art would reasonable conclude that the length of the ligand would inversely correlate with the reliability of producing neutralizing antibodies of said ligand because the longer ligands would have many more immunogenic epitopes and thus would produce a polyclonal antibody response with no guarantee that any of the antibodies would be able to antagonize the binding of the ligand to the receptor. The art teaches that conjugation of a small self peptide to a foreign T-cell helper epitope such as tetanus toxoid aids in the recognition of the fused peptide as "non-self". It is reasonable to conclude that the physical proximity of the peptide sequence to the "self" peptide is necessary for this recognition by the immune system. In the case of a larger tyrosine kinase receptor, or a larger tyrosine kinase receptor ligand, the amino acid sequence adjacent to the foreign peptide will be recognized as "non-self". However, there is no scientific basis for concluding that the processing of the entire protein comprising the foreign T-cell helper epitope by the host immune system will provide B-cell epitopes on antigen-presenting cells which would allow for the activation of B-cells which would secrete an antibody having the required neutralizing action on a large PTK ligand, such as HGF, or having the ability to antagonize a PTK receptor, such as EGFR. These large ligands and receptors comprise many potential antigenic epitopes to which a antibody might bind, but only a limited number of said epitopes will provide a binding site for an antibody that will result in the necessary neutralization or antagonistic activity. For instance, Lokker et al (J Biol Chem, 1997, Vol. 272, pp. 33037-33044) teach that anti-PDGF receptor antibodies generated in a foreign host include antibodies which inhibited receptor phosphorylation and mitogenic response and antibodies which did not, such as 2A1E2 and 1B5B11 versus 2G4D10 and 2H7C5 (page 33039, second column, lines 14-21 and page 33040, first column, lines 8-17). Gill et al (J Biol Chem, 1984, Vol. 259, pp. 7755-7760) teach that three types of monoclonal antibody generated against EGF receptors in foreign hosts have been described and include an IgM antibody which is an agonist for cell growth and competes with EGF for binding; a second group of Ab of different classes which are able to immunoprecipitate EGF receptors but do not effect EGF binding or elicits biological responses; and a third group of Ab block EGF binding to the EGF receptor, but the antibodies themselves

have a complex effect on cell growth which appear to mediate the stimulatory effect of EGF (page 7755, second column, lines 2-26). This reference serves to demonstrate that agonistic antibodies can be generated which serve to further activate rather than antagonize the PTK. It can be concluded that the interaction of an antibody with a large protein receptor is complex, because binding at different epitopes of said receptor will elicit different biological effects on said receptor and that it is possible to generate agonistic antibodies as well as antagonistic antibodies. By the same reasoning, the interaction between an antibody and a large protein is also complex: the antibody may bind to an area of the protein which would not inhibit contact between the ligand and the receptor. While the instant specification is enabled for the administration of a specific antibody which is known to be antagonistic to the receptor and inhibits the mitogenic effect of the receptor in the presence of the natural ligand, and also for the administration of a neutralizing antibody which binds to a PTK ligand, wherein the antibodies have been pre-screened for biological activity in vitro, the specification is not enabling for how to make said antibodies in a patient by eliciting an immune response against the receptor or large ligand. Given the lack of teachings in the specification for how to elicit the required antibodies in vivo by administration of the described vaccine, one of skill in the art would be subject to undue experimentation in order to make the claimed immunogenic combinations and carry out the claimed methods.

Applicant argues that immunization with ligands or receptors can be used to elicit the desired immune response in a patient. Applicant provides the reference of Birk et al to demonstrate that immunization with a large protein resulted in the same kinds of antibodies as immunization with different peptides. This has been considered but not found persuasive, because Birk et al does not teach how to specifically induce neutralizing antibodies and how to avoid the induction of agonistic antibodies. Applicant argues that Molina et al teach that growth factor receptors having TK activity can be used as antigens in vaccines. This has been considered but not found persuasive, because Molina et al is silent on the induction of antagonistic antibodies or the avoidance of agonistic antibodies. Applicant argues that Raimez et al teaches that immunization with Her-2 results in antibodies which block the binding of EGF to the receptor. This has been considered but not found persuasive. Raimez et al carries out the immunization in Freud's

adjuvant for the induction of a cellular immune response to immunization with ECD of the EGF receptor (page 4, lines 5-20) and is silent on the induction of antagonistic antibodies or the avoidance of agonistic antibodies.

(B) As drawn to the claims requiring antibodies having the same biding specificity as IOR-R3 or EGF-1

The specification lacks an enabling disclosure of how to make the hybridoma or other cell line which secretes the an antibody which is exactly the same as the IOR R3 or the EGF-1 antibodies. It is noted that in order to practice the claims requiring antibodies having the same binding specificities as the IOR-R3 or EGF-1 antibodies it would be necessary to have the IOR-R3 andEGF-1 antibodies available for comparison in order to assure that the claimed antibodies do indeed have the same binding specificity. It is recognized in the art that exact replication of a cell line is an unpredictable event. Clark (Protein Engineering of Antibody Molecules for Prophylactic and Therapeutic Applications in Man, 1993, page 1) states "The in vivo antibody response is heterogeneous and is made up of a large mixture of antibodies secreted from a polyclonal population of cells. In addition, because the differentiation of B cells involves the random rearrangements of gene segments and somatic mutation of these rearranged genes,....no two animals, even of an inbred strain will make an identical set of antibodies". It is unclear that one of skill in the art could derive antibodies identical to those claimed. Undue experimentation would be required to generate and screen all of the possible antibody and hybridoma species to obtained the claimed antibodies without a publicly available source of the cell line secreted the IOR R3 antibody. If deposits are made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney or record who has the authority and control over the conditions of deposit over his/her signature or registration number stating that the deposit has been accepted by an International Depository authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed from the depository as required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. If deposits are not made

under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the deposited hybridomas are producing the monoclonal antibodies IOR-R3 and EGF-1 described in the specification as filed and are the same as those deposited in the depository, stating that the deposited hybridomas are producing the identical monoclonal antibodies IOR-R3 and EGF-1 as described in the specification and were in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re: Lundak, 773 F. 2d.1216, 227 USPQ 90 (CAFC 1985) and 37 CRF 1.801-1.809 for further information concerning deposit practice.

Applicant argues that it is not necessary to have the IOR-R3 or EGF-1 antibodies because the claims require only similar antibodies. This has been considered but not found persuasive. In order to practice the claims it would be necessary to have the IOR-R3 and EGF-1 antibodies for reasons of comparison, without which one of skill in the art would not know if the same binding specificity had been attained.

All other rejections and objections as set forth in the previous Office action have been withdrawn in light of applicant's amendments.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/17/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER